Studies Investigating Potential Inhibitors of Novel Coronavirus (SARS-Cov-2) COVID-19

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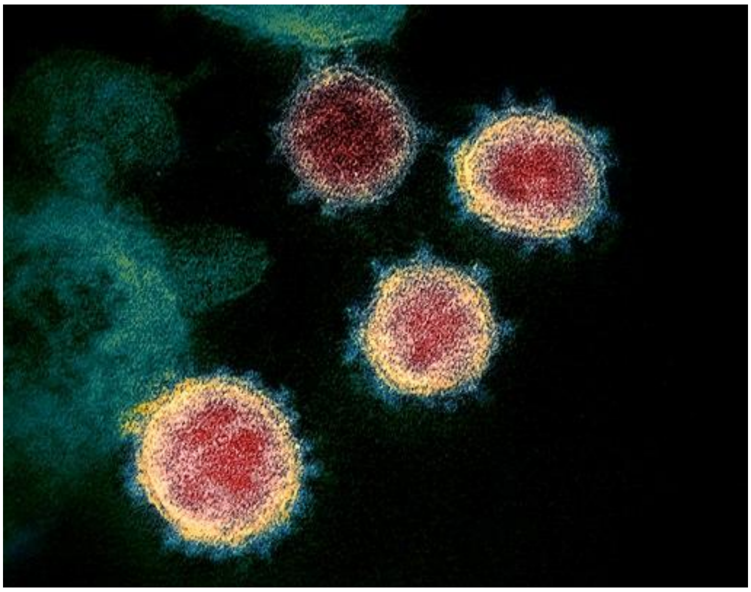

Fig. 1. Electron micrograph of SARS-CoV-2.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Fig. 1 [1]) is a viral pathogen leading to COVID-19 disease, first identified in Wuhan City, China, perhaps as early as November 2019 [2]. A number of patients in December 2019 were found to be epidemiologically associated with the Huanan seafood market (that also included non-aquatic animals on sale). COVID-19 is described by the World Health Organization (WHO) as a public emergency of international concern, leading to a world-wide pandemic affecting many countries globally. Currently, restrictive regimes in numerous countries focus on social distancing, testing and contact tracing in an attempt to curtail further rapid spread of the virus amongst members of the community. Positive cases of COVID-19 require self-isolation. A quarter of the world's population are now restricted, including the whole of the Indian sub-continent with approx. 1.3 billion people temporarily under 'lockdown'. This strategy has so far been successful in countries such as in China and South Korea, and there is evidence that strictly-enforced social distancing is starting to show fewer numbers of daily new infections in Italy, considered the original epicentre in Europe, now with the worst global death rate.

Not only has SARS-CoV-2 lead to a global pandemic, but major disruption in everyday lives, economic turmoil and uncertainty and even postponement of the 2020 Tokyo Olympic Games. Not since the Spanish flu just after the First World War, has the world faced such an unprecedented health challenge, requiring governments to rapidly build dedicated hospital facilities (e.g. with ventilators) to treat potentially large numbers of seriously ill COVID-19 patients during peak times.

SARS-CoV and MERS-CoV that spread in 2002 and 2013 respectively, have been associated with severe human illnesses, such as pneumonia and bronchiolitis [3]. SARS-CoV-2 is a pneumonia-inducing member of the same *Coronaviridae* family, thought to originate in bats and passed on to humans via an intermediate host, perhaps a pangolin. However, pangolin coronaviruses found to date only share at most 92% of their whole genomes with SARS-CoV-2 [4]; Pangolin-CoV is the second closest relative of SARS-CoV-2 behind RaTG13. The complete genome of SARS-CoV-2 has now been elucidated [5] and was closely related (with 88% genetic identity) to two bat-derived (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, but only 79% and 50% with SARS-CoV and MERS-CoV respectively [6].

So far [7], the outbreak in 2019–2020 has caused at least 438,749 confirmed infections and 19,675 deaths, rising daily. Many of the deaths are from cases with pre-existing conditions (more prevalent in the elderly), although also with a few teenagers and healthy younger adults in a minority of cases. No-one is not at risk of developing severe illness. Overall, the majority of those infected will only present with minor symptoms (e.g. a fever and persistent cough) or even appear asymptomatic, not requiring respiratory critical care (e.g. for severe pneumonia). Due to facile human-to-human viral transmission and the possible severity of the ensuing illness, the need for more effective prevention and suppression of COVID-19 is of upmost priority, ideally, avoiding it altogether via a reliable vaccine. SARS-CoV-2 is capable of using the human ACE2 receptor in alveolar cells as efficiently, if not more, than SARS-CoV, which may help to explain the human-to-human transmissibility of this virus [8]. The SARS ACE2 receptor was first identified in 2003 [9].

To date, there is no vaccine available, although there is considerable scientific and medical interest in the development of this [10]. In addition, current antivirals (e.g. previously tested against other SARS viruses) are under therapeutic investigation; the furin-like cleavage site in the spike glycoprotein S of SARS-CoV-2 (Fig. 2 [11]) may have implications for the viral life cycle and pathogenicity and its potential implication in the development of novel antivirals [12].

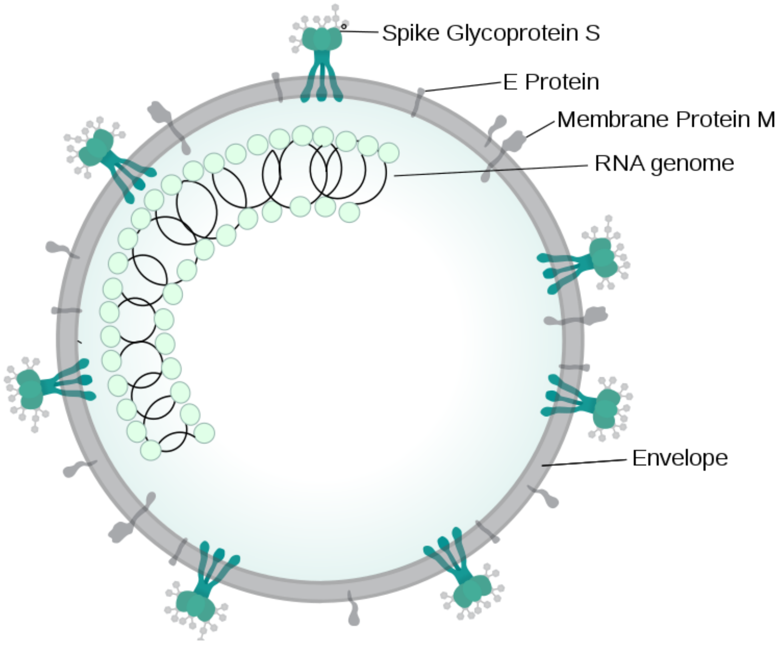

Fig. 2. Internal Representation of SARS-CoV-2.

This article mostly focuses on experimental treatment for COVID-19, based on several recent clinical studies with several known antivirals. Safe and effective vaccines at scale, however, are expected to take many months (probably a year or more). The list of potential antiviral and other biological therapies (e.g. use of antibodies) continues to grow, as more pharmaceutical companies, life sciences companies and research institutes try to seek inventive solutions to the global health crisis [2].

Antivirals

1. Remdesivir

Remdesivir (development code GS-5734) was developed by Gilead Sciences as a possible treatment for Ebola and Marburg virus infections [13], although was not generally successful with human Ebola disease. However, it shows broad spectrum activity against other single stranded RNA viruses such as SARS-CoV and MERS-CoV in laboratory tests. A recent study showed it could inhibit SARS-CoV-2, *in vitro* (with chloroquine) [14] and such is the desperate need to treat some fatally-ill COVID-19 patients, it is currently being used, on compassionate grounds, in clinical trials for COVID-19 and therefore to test its clinical efficiacy. One clinician suggested remdesivir showed an improvement [15], whilst another study found that remdesivir has no conclusive overall clinical effectiveness (to lessen viral count) and causes gastrointestinal symptoms [16]. More exhaustive studies are therefore required.

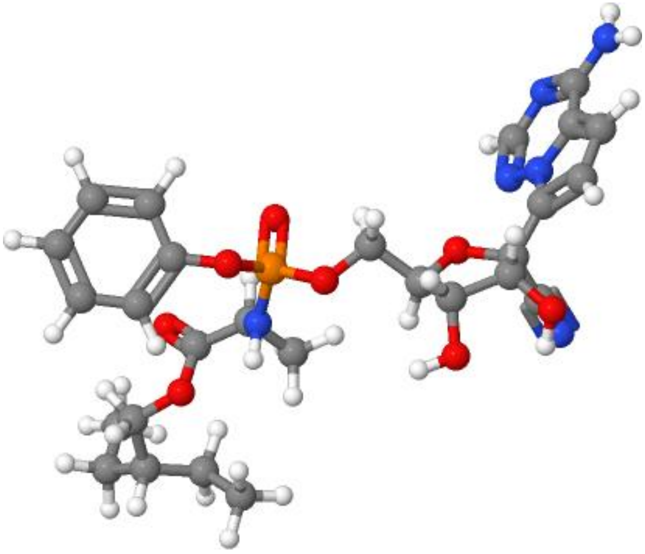

Fig. 3. Remdesivir.

The 3D structure of remdesivir (RDV) is shown (Fig. 3) (Jmol [17] visualisation). Chemical formula C27H35N6O8P. Legend: carbon atom grey; hydrogen, white; nitrogen, blue; oxygen, red; phosphorous, yellow. IUPAC name (2S)-2-{(2R,3S,4R,5R)-[5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]phenoxy-(S)-phosphorylamino}propionic acid 2-ethyl-butyl ester. The molecule contains several aromatic rings with delocalised π bonding.

Remdesivir is a prodrug, which is metabolised to the active triphosphorylated 1′-cyano-substituted adenine C-nucleoside ribose analogue GS-441524 (Figs. 4 and 5) that targets viral RNA-dependent RNA polymerase. An effective nucleoside analogue must evade proofreading (by 3′-5′ exoribonuclease) to successfully interfere with CoV RNA synthesis for better clinical efficiacy. It is enzymatically converted into the triphosphorylated active form. GS-441524 was also found to inhibit [18, 19] feline infectious peritonitis (FIP) virus, another coronavirus.

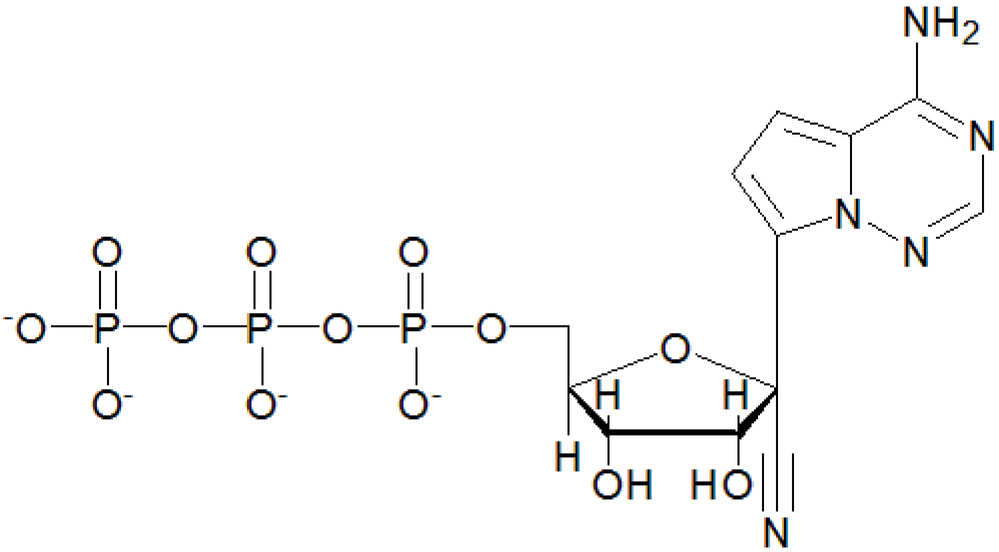

Fig. 4. Triphosphorylated GS-441524.

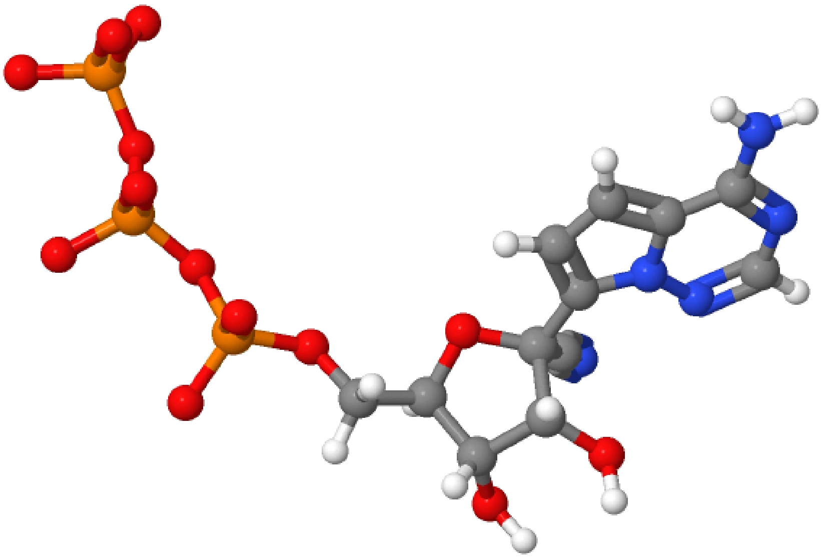

Fig. 5. Triphosphorylated GS-441524 in 3D. Legend: carbon, grey; hydrogen, white; phosphorous, yellow; oxygen, red.

An energy minimum for GS-441524 was determined (Fig. 6). GAMESS [20] semi-empirical PM6 energy minimum (no imaginary frequencies). R-PM6 heat of formation = -62.61 kcal/mol. Legend: carbon, grey; hydrogen, white; nitrogen, blue; oxygen, red. O-C-C=C torsion angle = -12.1 degrees.

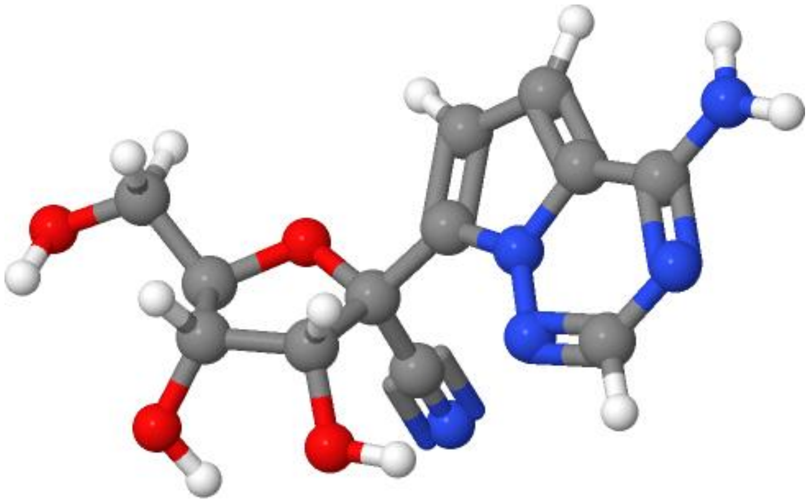

Fig. 6. GS-441524

2. Plaquenil

A COVID-19 clinical trial using anti-malarial (±)-hydroxychloroquine (HCQ) shows promise [21] for viral load reduction/disappearance, especially when combined with azithromycin (to prevent bacterial super-infection under daily electrocardiogram control). The study, however, was initially criticised for its methodology [22]. HCQ is also known as Plaquenil (HCQ sulfate). HCQ sulfate was found to be more potent than chloroquine *in vitro* in inhibiting SARS-CoV-2 [23], and an earlier study reveals its inhibitory effects with SARS-CoV too [24]. The authors propose that the immunomodulatory effect of HCQ also may be useful in controlling the cytokine storm that occurs late-phase in critically ill SARS-CoV-2 infected patients

The HCQ 3D molecular structure is shown (Fig. 7)(free base). Firefly 8.2.0 [25] PM3 energy minimum (no imaginary frequencies). Heat of formation = -29.41 kcal/mol. C-N-C=C torsion angle = 72.09 degrees. Legend: carbon atom: grey; hydrogen, white; nitrogen, blue; oxygen, red; chlorine, green.

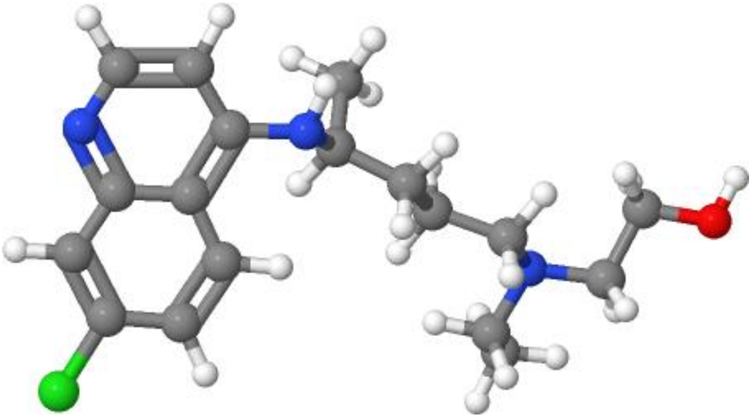

Fig. 7. Hydroxychloroquine.

3. Favipiravir

In an experimental study [26], Favipiravir was found to be effective in the treatment of COVID-19, reducing viral clearance time to 4 days in 91.4% of the group. It is a broad spectrum antiviral, active against RNA viruses and is metabolised to favipiravir-ribofuranosyl-5'-triphosphate, thought to inhibit viral RNA-dependent RNA polymerase [27]. According to the Chinese study [26], more than 16% of patients developed acute respiratory distress syndrome, and the fatality ratio was about 1%–2%.

Favipiravir 3D geometry is shown (Fig. 8). Firefly 8.2.0 DFT B3LYP 6-311G(d) energy minimum (no imaginary frequencies). Total energy = -607.6653 Hartrees. Legend: carbon atom; grey; hydrogen, white; nitrogen, blue; oxygen, red; fluorine, pale green. It is an extensively delocalised aromatic molecule. IUPAC name 6-fluoro-3-hydroxypyrazine-2-carboxamide (C5H4FN3O2).

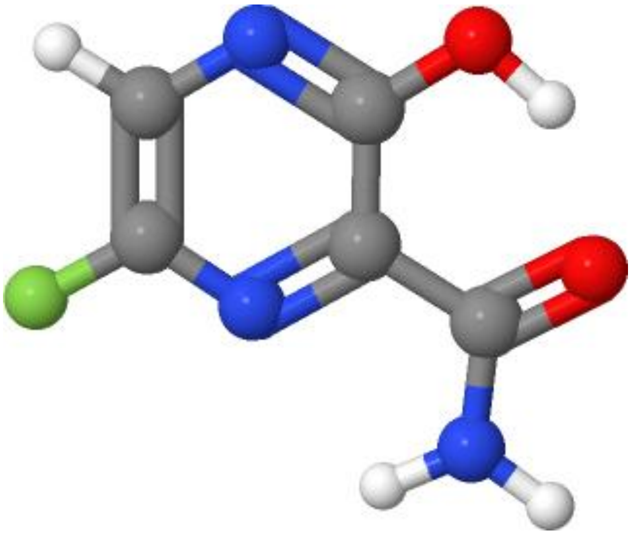

Fig. 8. Favipiravir.

Computer-Aided Design (CADD) of Target Therapies for COVID-19

Combined structure-assisted drug design, virtual drug screening and high-throughput screening is being used to identify drug leads that target the COVID-19 main protease (M^{pro}) enzyme. M^{pro} plays a pivotal role in viral gene expression and replication through the proteolytic processing of CoV replicase polyproteins [28] and is an attractive target for antiviral drug design. A mechanism-based inhibitor, N3 (Fig. 9), has been identified by computer-aided design and the crystal structure of COVID-19 virus M^{pro} in complex with N3 to 2.1-Å resolution [29] has been determined (Fig. 10)[30]. The authors , then, through a combination of structure-based virtual and high-throughput screening, assayed over 10,000 drugs and pharmacologically active compounds as potential inhibitors of M^{pro} and six (ebselen, disulfiram, tideglusib, carmofur, shikonin, PX-12) inhibit M^{pro} with 44 IC_{50} values ranging from 0.67 to 21.4 µM.

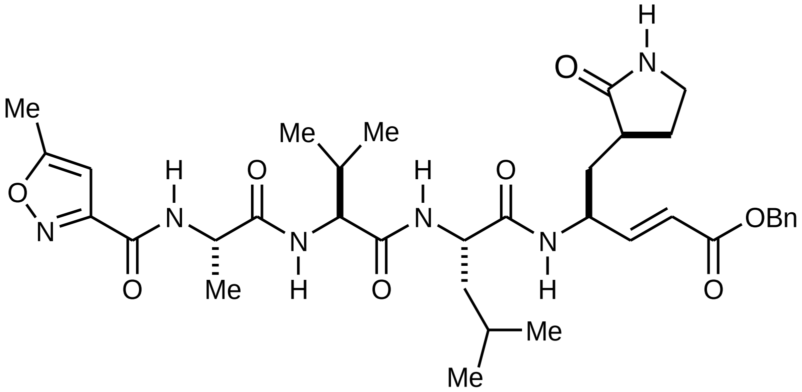

Fig. 9. Structure of inhibitor N3.

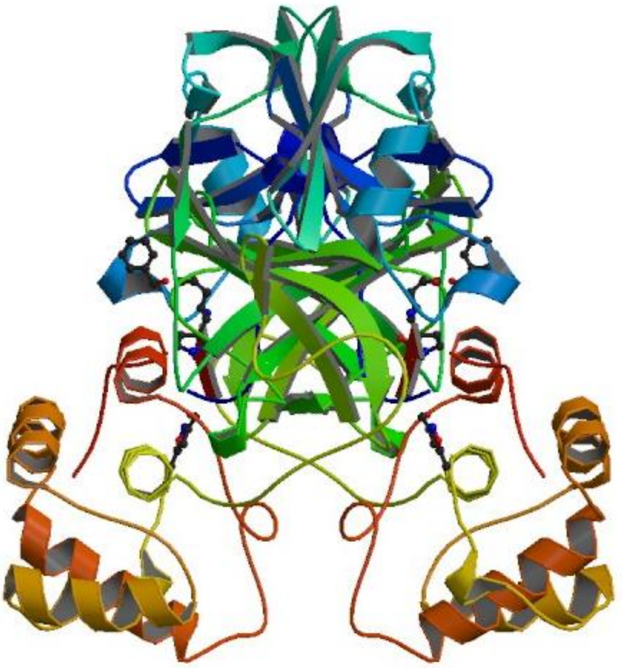

Fig. 10. COVID-19 virus M^{pro} in complex with N3 [28]

A Chinese research team [31] has also identified, using virtual docking procedures, up to 10 commercial medicines that may form hydrogen bounds to key residues within the binding pocket of SARS-CoV-2 M^{pro} and may have higher mutation tolerance compared to lopinavir/ritonavir.

With the rapid technological developments in A.I., generated deep learning approaches to potential SARS-CoV-2 3C-like protease inhibitors are being developed by Insilco Medicine based in Hong Kong [32]. Deep generative models can utilise large datasets for training and perform *in silico* design of *de novo* molecular structures with pre-defined properties [32]. According to the authors [33], the emergence of resistance to existing antiviral drugs and re-emerging viral infections are the biggest challenges in antiviral drug discovery. Insilico's pipeline consists of target discovery, small molecule drug discovery and predictors of clinical trial outcomes. The distributed pipeline was run for 72 hours on an internal computing cluster with 64 NVIDIA Titan V GPUs and the highest-ranking output structures were selected for further analysis.

Conclusion

An increasing number of reports in the literature are starting to investigate whether current antivirals would be effective against COVID-19. Although it is early days, some antivirals show promise, and first choice seems to be inhibitors of previous SARS-like coronaviruses. There are sometimes mixed messages from different clinical trials/studies (despite often better initial success *in vitro*) and more exhaustive studies are therefore warranted. Computer-aided design and medicinal chemistry (e.g. molecular docking) will continue to play an important role in potential future inhibitors, even making use of deep learning , where appropriate. It is hoped that future antivirals and target therapies show better overall statistical efficiency and drug resistance profiles, but, from general public consensus, it is seems that a reliable vaccine is likely to be the way forward with COVID-19.

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Supplementary Information: Cartesian Co-ordinates

GS-441524 (PM6 energy minimum, *in vacuum*)

O	8.0	-2.4408460533	-2.4551547184	1.0122031082
C	6.0	-1.1745664127	-1.7977217443	1.0372769021
C	6.0	-0.2755419940	-2.3529416485	-0.0734597110
H	1.0	-0.8663620182	-2.5838160391	-0.9899228039
O	8.0	0.6272694081	-1.2532167314	-0.3982823375
C	6.0	1.9036478061	-1.7821684740	-0.8267620861
C	6.0	1.8751713685	-1.8878715037	-2.3011407437
C	6.0	2.9385656526	-0.7916968973	-0.3966837786
C	6.0	2.7567185604	0.5297677760	0.0816175536
C	6.0	4.0147182876	1.1000093591	0.3283644337
C	6.0	4.9938918973	0.1355946966	0.0026098410
C	6.0	6.4357236471	0.0571040580	0.0053472344
N	7.0	7.0723916256	-1.0854882226	-0.3969594802
C	6.0	6.2763003959	-2.1448077260	-0.7923144974
N	7.0	4.9310402520	-2.1776239827	-0.8311940035
N	7.0	4.3030764409	-1.0294171098	-0.4421878537
N	7.0	7.2043488159	1.1102072808	0.4246436679
C	6.0	2.0436407032	-3.1875665140	-0.1369904148
H	1.0	2.7772469706	-3.1593325732	0.6955582930

O	8.0	2.4115611056	-4.1919103619	-1.0689947719
C	6.0	0.6115662362	-3.5556696066	0.3394951379
H	1.0	0.5777904323	-3.7650543744	1.4321146662
O	8.0	0.1135330560	-4.7439261046	-0.2402394614
H	1.0	-1.4306300590	-0.7344112834	0.8415774006
H	1.0	-0.7253965104	-1.8840228560	2.0413093220
H	1.0	6.8114872912	-3.0589622944	-1.1092600714
H	1.0	6.7918386866	1.9920161173	0.6735050560
H	1.0	8.2132291805	1.0486819235	0.3898371270
H	1.0	3.3483399125	-4.0519746987	-1.3695284825
H	1.0	0.5134813891	-4.9078265910	-1.1370466366
H	1.0	1.7925515248	0.9906982580	0.2190087435
H	1.0	4.2037220866	2.0896073105	0.6956289583
N	7.0	1.8401870278	-1.9513663651	-3.4515578802
H	1.0	-2.3304567134	-3.4253383588	1.1288775690

Hydroxychloroquine (PM3 energy minimum, *in vacuum*)

CL	17.0	-6.6996456298	1.9348082381	1.0235551135
O	8.0	4.6447588884	-4.6670509525	-1.5977368478
N	7.0	1.5476045365	-2.6862065229	-1.8339819446
N	7.0	-0.0076302687	1.8249044898	2.2030683785
N	7.0	-2.8998184755	4.9288803053	2.5242170533
C	6.0	0.7679718596	-0.0978767762	0.8811450241
C	6.0	0.9153659894	-0.6741819221	-0.5184445424
C	6.0	0.3502181724	1.3782694911	0.8193842286
C	6.0	1.4982365783	-2.0808270467	-0.4701762498
C	6.0	2.4261159010	-3.8912511700	-1.8815211999

C	6.0	1.4587341104	2.2212519184	0.1964806258
C	6.0	0.1853760564	-2.9607625236	-2.3815449105
C	6.0	-0.9898493137	2.8792367586	2.2805342617
C	6.0	3.8938530016	-3.4804562734	-1.7188244372
C	6.0	0.2375593111	-3.2466209964	-3.8691125516
C	6.0	-2.3659665703	2.6028943012	1.9744560312
C	6.0	-0.6396396386	4.1375368610	2.7213694519
C	6.0	-3.2933412872	3.6642523426	2.0938319820
C	6.0	-2.8461475666	1.3232280142	1.5890632290
C	6.0	-1.6324253505	5.1448046709	2.8361268853
C	6.0	-4.6664000784	3.4605519771	1.7876479304
C	6.0	-4.1724073555	1.1319941798	1.3053083884
C	6.0	-5.0795233119	2.2122302499	1.3966080562
H	1.0	0.0197784374	-0.6836461312	1.4538140869
H	1.0	1.7221033060	-0.2029417756	1.4367444407
H	1.0	1.5568801503	0.0022335989	-1.1285251157
H	1.0	-0.0704262286	-0.6946892985	-1.0379746132
H	1.0	-0.5687476510	1.4637708189	0.1849343897
H	1.0	0.9195141725	-2.7149271274	0.2367118040
H	1.0	2.5448286917	-2.0570200880	-0.0888271028
H	1.0	0.8153800344	2.0736310778	2.7109625094
H	1.0	2.1379829677	-4.6384181837	-1.1102820350
H	1.0	2.2621008987	-4.3796090164	-2.8690607636
H	1.0	2.3553937542	2.2711223454	0.8300498649
H	1.0	1.7670927045	1.7731122652	-0.7637004309
H	1.0	1.1328161540	3.2500371942	-0.0013657085
H	1.0	-0.3015100453	-3.8020242895	-1.8423484534

H	1.0	-0.4312246303	-2.0565243122	-2.1763725023
H	1.0	4.2426655737	-2.8834564447	-2.5833946598
H	1.0	4.0191425430	-2.8508252820	-0.8075907646
H	1.0	-0.7501893257	-3.5424802104	-4.2434302457
H	1.0	0.5624997346	-2.3719765980	-4.4470757763
H	1.0	0.9426348943	-4.0658745405	-4.0913154713
H	1.0	0.3935331735	4.3910015716	2.9871315021
H	1.0	-2.1508973853	0.4750250353	1.5358002921
H	1.0	-1.3830851409	6.1549367587	3.1820786715
H	1.0	-5.3775522803	4.2919950627	1.8692981718
H	1.0	-4.5496469858	0.1463397999	1.0107190063
H	1.0	5.5559329244	-4.4085918446	-1.6083550525

Favipiravir (DFT B3LYP 6-311G(d) energy minimum, *in vacuum*)

O	8.0	0.9390997780	2.1848388045	-0.7405979592
C	6.0	0.0524948880	1.2522298677	-0.4160374224
N	7.0	-1.2376157916	1.5705537247	-0.5744735660
C	6.0	-2.1397716101	0.6573106408	-0.2568204259
C	6.0	-1.7543862279	-0.5973144226	0.2276774528
F	9.0	-2.6947704180	-1.5012887965	0.5412950919
N	7.0	-0.5068463444	-0.9358781838	0.3916781785
C	6.0	0.4223473057	-0.0226837867	0.0749384707
C	6.0	1.8608694910	-0.3812908977	0.2523891068
O	8.0	2.7540888194	0.4266172723	-0.0230058864
N	7.0	2.0968072052	-1.6191601019	0.7224674075
H	1.0	1.8369364727	1.8117388871	-0.5721612802
H	1.0	-3.1890658054	0.9073885122	-0.3821334501

H	1.0	1.3270393681	-2.2350399006	0.9293953857
H	1.0	3.0470628695	-1.9190316195	0.8632888964

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Abstract

Emergence of COVID-19 in China in late 2019 has now lead to a global pandemic. Several recent reports in the literature using antivirals and other potential enzyme inhibitors show early promise in clinical studies, albeit sometimes with mixed success rates. This article very briefly focuses on the use of remdesivir, hydroxychloroquine and favipiravir, presenting their 3D chemical structures and important biological interactions. Computer-aided design and medicinal chemistry will continue to play an important role in the development of potential future protease inhibitors.

Keywords: SARS, coronavirus, SARS-Cov-2, 2019-nCoV, COVID-19, antivirals, pandemic.

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